UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/726,919	12/02/2003	Michael P. Caulfield	034827-9103	4734

30542 7590 03/04/2005

FOLEY & LARDNER
P.O. BOX 80278
SAN DIEGO, CA 92138-0278

EXAMINER	
CORDERO GARCIA, MARCELA M	
ART UNIT	**PAPER NUMBER**
1654	

DATE MAILED: 03/04/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/726,919	CAULFIELD ET AL.	
	Examiner	Art Unit	
	Marcela M Cordero Garcia	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-43 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-43 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 06/04 and 10/04.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claim Objections

Claim 33 is objected to because of the following informalities: there are duplicate claims numbered 33. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-2, 11-12, 22 and 33 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for, e.g., SELDI and APPI ionization of testosterone ions to produce a molecular ion (m/z 289.1 $\pm$ 0.5) or the fragments of m/z 109.2 $\pm$ 0.5 and 96.9 $\pm$ 0.5, does not reasonably provide enablement for MALDI or electrospray (ES) ionization. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Claims 12, 22, and 33 are directed to ionizing testosterone using MALDI and ES ionization in order to produce the ions described above, which correspond to the testosterone $[M+H]^+$ molecular ion and two testosterone fragments. However, the specification fails to teach how to make such ions using MALDI or ES. The mass

spectrometry research area is a highly unpredictable and undeveloped field in regards to this aspect, and the skill in the art is high. Griffiths et al. (Rapid Comm Mass Spectrom, 2003) teach that neutral oxosteroids --such as testosterone-- (see, e.g., Scheme I, page 925) are not readily ionized by electrospray ionization or MALDI (see, e.g, abstract, page 924).

The specification fails to disclose the method wherein the ionization is carried out via MALDI or ES and how it would use it to make the testosterone ions in the instantly claimed invention. Based on the state of the art as indicated above, utilizing the complete scope of the instantly claimed method would require of undue experimentation in order to determine how to utilize MALDI or ES ionization to create any of the ions required for carrying out the instantly claimed method. In view of the quantity of experimentation necessary to determine the above parameters, the lack of direction or guidance presented, the absence of working examples for the claimed ionization methods, the breadth of the claims, and the unpredictable and undeveloped state of the art with respect to ionization of testosterone using MALDI or ES, it would require undue experimentation for one skilled in the art to practice the entire scope of the claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 12 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 12 is rendered vague and indefinite because the claim 11 method, from which this claim is dependent, is drawn to testosterone ionized by APPI, which does not provide antecedent basis for testosterone being ionized via electrospray (ES).

Claim Rejections - 35 USC § 102

For the art rejection below, please note that the reference below teaches the steroisomeric forms of testosterone "17-α testosterone" and "17-β testosterone".

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-3, 10, 14, 18, 21, 25, 36 and 40-42 are rejected under 35 U.S.C. 102(b) as being anticipated by Draisci et al. (Journal of Chromatography A, 2000).

Draisci et al. teach a method for determining the presence or amount of testosterone in a test sample comprising,

(a) ionizing testosterone from said test sample to produce one or more testosterone ions detectable by mass spectrometry having a mass/charge ratio selected from 289.1 $\pm$ 0.5, 109 $\pm$ 0.5 and 96.9 $\pm$ 0.5 (see, e.g., Figs. 1-2, page 513, column 2); and

(b) detecting the presence or amount of the testosterone ion(s) by mass spectrometry wherein the presence or amount of the testosterone ion(s) is related to the presence or amount of testosterone in the test sample (see, e.g., pages 513-514 and Figs. 3-4)

In addition, the reference teaches the step (a) comprising:

-ionizing said testosterone ion(s) from said sample to provide a precursor ion having a mass/charge ratio (m/z) of about 289.1 $\pm$ 0.5

-isolating the precursor ion by mass spectroscopy; and effecting a collision between the isolated precursor ion and an inert collision gas to produce one or more testosterone ions detectable by mass spectrometry having a mass/charge ratio of 109.2 $\pm$ 0.5 and 96.7 $\pm$ 0.5 (see, e.g. page 514, column 2, lines 5-6 and Fig. 2).

Therefore, the reference is deemed to anticipate the instant claims above.

Claims 1-3, 10, 14, 17-18, 21, 25, 33, 36 and 40-42 are rejected under 35 U.S.C. 102(b) as being unpatentable over Tiller et al. (Journal of Chromatography A, 1997).

Tiller et al. teach a method for determining the presence or amount of testosterone in a test sample comprising,

(a) ionizing testosterone from said test sample to produce one or more testosterone ions detectable by mass spectrometry having a mass/charge ratio selected from 289.1 $\pm$ 0.5, 109 $\pm$ 0.5 and 96.9 $\pm$ 0.5 (see Fig. 3 and pages 121-122); and

(b) detecting the presence or amount of the testosterone ion(s) by mass spectrometry wherein the presence or amount of the testosterone ion(s) is related to the

presence or amount of testosterone in the test sample (see, e.g., page 123, column 1, lines 3-11)

In addition, the reference teaches the step (a) comprising:

-ionizing said testosterone ion(s) from said sample to provide a precursor ion having a mass/charge ratio (m/z) of about 289.1 $\pm$ 0.5

-isolating the precursor ion by mass spectroscopy; and effecting a collision between the isolated precursor ion and an inert collision gas to produce one or more testosterone ions detectable by mass spectrometry having a mass/charge ratio of 109.2 $\pm$ 0.5 and 96.7 $\pm$ 0.5 (see, e.g. page 123, column 1).

Therefore, the reference is deemed to anticipate the instant claims above.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-3, 10-11, 13-15, 17-18, 21-25, 33-36 and 40-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tiller et al. (Journal of Chromatography A, 1997) in view of Merchant et al. (Steroids, 1988, citation A16 IDS of June 1, 2004) or in view of Robb et al. (Anal Chem, 2000, citation A19 IDS of June 1, 2004) as evidenced by Brekenfeld et al. (US 6,410,913).

Tiller et al. beneficially teach a method for determining the presence or amount of testosterone in a test sample comprising,

(a) ionizing testosterone from said test sample to produce one or more testosterone ions detectable by mass spectrometry having a mass/charge ratio selected from 289.1 $\pm$ 0.5, 109 $\pm$ 0.5 and 96.9 $\pm$ 0.5 (see, e.g., Figs. 1-2, page 513, column 2); and

(b) detecting the presence or amount of the testosterone ion(s) by mass spectrometry wherein the presence or amount of the testosterone ion(s) is related to the presence or amount of testosterone in the test sample (see, e.g., pages 513-514 and Figs. 3-4)

In addition, the reference teaches the step (a) comprising:

-ionizing said testosterone ion(s) from said sample to provide a precursor ion having a mass/charge ratio (m/z) of about 289.1 $\pm$ 0.5

-isolating the precursor ion by mass spectroscopy; and effecting a collision between the isolated precursor ion and an inert collision gas to produce one or more

testosterone ions detectable by mass spectrometry having a mass/charge ratio of 109.2 ± 0.5 and 96.7 ± 0.5 (see, e.g. page 514, column 2, lines 5-6 and Fig. 2).

Tiller et al. do not teach the use of APPI or SELDI ionization methods.

Merchant et al. beneficially teach that SELDI ionization produces abundant $[M+H]^+$ ions (i.e., m/z 289.1 for testosterone).

Robb et al. beneficially teach that APPI ionization produces abundant $[M+H]^+$ ions (i.e., m/z 289.1 for testosterone) (see, e.g., Figure 3, page 3657).

Brekenfeld (US 6,410,913) evidences use of nitrogen, argon and helium as collision gases used in tandem mass spectrometer (see, e.g., column 7, last paragraph).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to utilize the method taught by Tiller et al., which is based on the [M+H]+ of testosterone, with any other ionization methods which produce abundant [M+H]+ ions such as SELDI and APPI. The adjustment of particular conventional working conditions (e.g., determining appropriate ionization and temperature conditions within the ionization chamber where the testosterone ions are produced, utilizing a specific type of tandem mass spectrometer such as MS/MS/TOF to carry out the analysis or using nitrogen as collision gas) is deemed merely a matter of judicious selection and routine optimization that is well within the purview of the skilled artisan.

Thus, the invention as a whole is prima facie obvious over the references, especially in the absence of evidence to the contrary.

Claims 1-3, 10, 14, 17-18, 25-28, 33, 36-43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tiller et al. (Journal of Chromatography A, 1997) in view of Williams et al. (Journal of Mass Spectrometry, 1999, reference A3 in the IDS of October 12, 2004) as evidenced by Lewis et al. (DOT/FAA/AM-00/20 Final Report, Office of Aviation Medicine, 2000)

Tiller et al. beneficially teach a method for determining the presence or amount of testosterone in a test sample comprising,

(a) ionizing testosterone from said test sample to produce one or more testosterone ions detectable by mass spectrometry having a mass/charge ratio selected from 289.1 $\pm$ 0.5, 109 $\pm$ 0.5 and 96.9 $\pm$ 0.5 (see, e.g., Figs. 1-2, page 513, column 2); and

(b) detecting the presence or amount of the testosterone ion(s) by mass spectrometry wherein the presence or amount of the testosterone ion(s) is related to the presence or amount of testosterone in the test sample (see, e.g., pages 513-514 and Figs. 3-4)

In addition, the reference teaches the step (a) comprising:

-ionizing said testosterone ion(s) from said sample to provide a precursor ion having a mass/charge ratio (m/z) of about 289.1 $\pm$ 0.5

-isolating the precursor ion by mass spectroscopy; and effecting a collision between the isolated precursor ion and an inert collision gas to produce one or more testosterone ions detectable by mass spectrometry having a mass/charge ratio of 109.2 $\pm$ 0.5 and 96.7 $\pm$ 0.5 (see, e.g. page 514, column 2, lines 5-6 and Fig. 2).

Tiller et al. teach the use of a reference sample, d_2 testosterone, but do not the specific reference sample 2,2,4,6,6-d_5 testosterone.

Williams et al. beneficially teach 2,2,4,6,6-d_5 testosterone as a reference sample to study via mass spectrometry the fragmentation patterns of 2,2,4,6,6-d_5 testosterone and teach the masses 294.1 $\pm$ 0.5, 113.2 $\pm$ 0.5 and 99.9 $\pm$ 0.5 (corresponding to the isotopically equivalent fragments of those analyzed for the non-deuterated testosterone, i.e., 289.1 $\pm$ 0.5, 109 $\pm$ 0.5 and 96.9 $\pm$ 0.5). See, e.g., Table 2 and Table 3.

Lewis et al. evidence that quantitation of analytes may be accomplished by summing the intensities of the highest abundance ions in the MS/MS spectrum (see, e.g., page 9, column 1, lines 1-4).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use the method beneficially taught by Tiller et al. with the reference sample 2,2,4,6,6-d_5 testosterone because, as beneficially taught by Williams et al., 2,2,4,6,6-d_5 testosterone is a reference sample whose fragmentation ion pattern upon collisional induced dissociation parallels the fragmentation pattern of testosterone (see, e.g., page 199 and Tables 2-3) and therefore acts as internal standard in quantitation methods. The adjustment of particular conventional working conditions (i.e. applying an analogous method to the daughter ions of the isotopic analog than the one used for the non-enriched testosterone) is deemed merely a matter of judicious selection and routine optimization that is well within the purview of the skilled artisan.

Thus, the invention as a whole is prima facie obvious over the references, especially in the absence of evidence to the contrary.

Claims 1-10, 14, 17-21, 25, 33, 36 and 40-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tiller et al. (Journal of Chromatography A, 1997) in view of Zimmer et al. (Journal of Chromatography A, 1999, citation A22 in the IDS of June 1, 2004) and in view of Quinn et al. (US 5,795,469, citation A2 in the IDS of June 1, 2004) and in further view of Starcevic et al. (Journal of Chromatography B, 2003, citation A2 in IDS of October 12, 2004) as evidenced by Ropero-Miller et al (Journal of Analytical Toxicology, 2002).

Tiller et al. beneficially teach a method for determining the presence or amount of testosterone in a test sample comprising,

(a) ionizing testosterone from said test sample to produce one or more testosterone ions detectable by mass spectrometry having a mass/charge ratio selected from 289.1 $\pm$ 0.5, 109 $\pm$ 0.5 and 96.9 $\pm$ 0.5 (see, e.g., Figs. 1-2, page 513, column 2); and

(b) detecting the presence or amount of the testosterone ion(s) by mass spectrometry wherein the presence or amount of the testosterone ion(s) is related to the presence or amount of testosterone in the test sample (see, e.g., pages 513-514 and Figs. 3-4)

In addition, the reference teaches the step (a) comprising:

-ionizing said testosterone ion(s) from said sample to provide a precursor ion having a mass/charge ratio (m/z) of about 289.1 $\pm$ 0.5

-isolating the precursor ion by mass spectroscopy; and effecting a collision between the isolated precursor ion and an inert collision gas to produce one or more testosterone ions detectable by mass spectrometry having a mass/charge ratio of 109.2 ± 0.5 and 96.7 ± 0.5 (see, e.g. page 514, column 2, lines 5-6 and Fig. 2).

Tiller et al. do not teach the use of HTLC (high turbulence liquid chromatography) to purify the sample before the mass spectrometric step.

Zimmer et al. beneficially teach the use of an automated inline HTLC separation coupled to MS-MS (tandem mass spectrometry) and that HTLC is a pioneering technique for the direct analysis of even highly protein bound drugs from crude plasma, and the use of two columns, one for extraction and one for analytical purposes.

Zimmer et al. do not specifically teach a particle size of about 4 μm nor a C_{12} extraction column or deproteinating testosterone prior to analysis.

Quinn et al. teach a particle size of about 4 μm for use in HTLC (see, e.g., column 5, lines 50-54) and the use on inline filter and automated injector (see, e.g. column 10, lines 34-36 and lines 63-65).

Starcevic et al. teach that testosterone forms highly protein bound drugs from crude plasma (see, e.g. page 197, last paragraph and page 198, first paragraph).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to utilize the HTLC-MS-MS method beneficially taught by Zimmer et al. and by Quinn et al. with testosterone because it was known in the art that testosterone in plasma was highly bound to proteins (see Starcevic et al., e.g., page 197, last paragraph and page 198, first paragraph). The adjustment of particular

conventional working conditions [e.g., determining appropriate column packing for the extraction column, using deproteination techniques commonly known in the art as evidenced by Ropero-Miller et al. (see, e.g., abstract) and automating all the steps in an inline fashion within such mass spectrometric method] is deemed merely a matter of judicious selection and routine optimization that is well within the purview of the skilled artisan.

Thus, the invention as a whole is prima facie obvious over the references, especially in the absence of evidence to the contrary.

Information Disclosure Statement

The information disclosure statements (IDSs) submitted on June 1st 2004 and October 12, 2004 were filed after the mailing date of the application on December 2, 2003. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statements have been considered by the examiner.

Conclusion

No claim is allowed.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marcela M Cordero Garcia whose telephone number is (571) 272-2939. The examiner can normally be reached on M-Th 7:30-6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on (571) 272-0974. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Marcela M Cordero Garcia
Patent Examiner
Art Unit 1654

MMCG 02/05

CHRISTOPHER R. TATE
PRIMARY EXAMINER